



General

Guideline Title

Renal cell carcinoma.

Bibliographic Source(s)

Alberta Provincial Genitourinary Tumour Team. Renal cell carcinoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 May. 14 p. (Clinical practice guideline; no. GU-003). [50 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Genitourinary Tumour Team. Renal cell carcinoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Jan. 15 p. (Clinical practice guideline; no. GU-003). [56 references]

Recommendations

Major Recommendations

A detailed description of the staging can be found in the Appendix of the original guideline document.

Stage T1-3, N0

Indications include imaging suspicious for primary renal malignancy localized to the kidney or immediate surrounding structures.

Management

Staging

- History and physical examination (Hx/Px) (lymph node survey)
- Chest x-ray (CXR)
- Computed tomography (CT) scan of abdomen/pelvis with contrast (or magnetic resonance imaging [MRI])
- Complete blood count (CBC), creatinine (Cr), calcium (Ca), liver function tests (LFTs)
- Biopsy is an option as part of active observation or prior to ablative therapy
- Optional tests:
 - CT chest if T2 or T3
 - Bone scan if T2 or T3 or alkaline phosphatase is elevated

First-line Therapy

[illegible]

CXR	3	6	12	18	24	30	36	48	60	72
CT abdomen	X	X	X	X	X	X	X	X	X	X

If relapses are to occur, they may happen early or very late. Therefore, the necessary duration of follow-up beyond these guidelines is unclear and should be directed based on relapse risk.

Stage T4, N1-2, M+ (Motzer et al., "Activity," 2006)

Indications include locally advanced, unresectable cancer or metastatic disease.

Management (Atkins, 2005)

Staging

- CBC, calcium, LFTs, renal function test.
- CT abdomen, pelvis, thorax and other imaging procedures as clinically indicated.

First-line Therapy

Sunitinib (Motzer et al., "Sunitinib," 2006; Motzer et al., 2007; Rini et al., 2006; Rini et al., 2007; Houk et al., 2007; Telli et al., 2008)

- Indication:
 1. First-line therapy for metastatic RCC based on phase III data
 2. Second-line therapy for metastatic RCC based on phase II data after cytokine failure
- Dose and Schedule:
 - Starting dose at 50 mg/day orally for 4 weeks followed by a 2-week rest period for a 6-week treatment cycle
- Toxicity:
 - Physicians must be aware of the toxicity profile of sunitinib and follow patients accordingly with experienced nursing support. Patients should be assessed every cycle for treatment tolerance.
 - Sunitinib should be dosed to maximum treatment tolerance as there is evidence that higher area under the curve (AUC) leads to higher response rates (Houk et al., 2007).
 - Cardiotoxicity has become an issue in patients with pre-existing coronary artery disease (CAD) or CAD risk factors.
 - Monitoring of ejection fraction (EF) should be considered in high risk or symptomatic patients, but routine monitoring in all patients is not indicated (Telli et al., 2008).
- Efficacy Assessment:
 - Imaging of involved sites every 2 cycles initially then as clinically indicated. Patients responding with either stable disease or an objective response may continue therapy. Treatment is to be continued until disease progression or patient intolerance.

Temsirolimus (Escudier, 2010; Hudes et al., 2007)

- Indication:
 - First-line therapy for metastatic RCC in poor-prognosis patients
 - Temsirolimus has been shown in a phase III trial of poor-prognosis patients with clear cell and non-clear cell RCC to improve overall survival
- Dose and Schedule:
 - Delivered as 25 mg intravenous (IV) weekly
- Toxicity:
 - Treatment side effects and laboratory abnormalities should be initially monitored weekly, then every 2 weeks. This follow-up interval may be extended if clinically appropriate.
- Efficacy Assessment:
 - Efficacy should be assessed every 8 weeks.

Pazopanib

- Indication:
 - First-line therapy for metastatic RCC based on phase III data
- Efficacy Assessment:

- Pending results of the COMPARZ clinical trial comparing pazopanib to sunitinib, pazopanib is only indicated in those patients that may not be candidates for sunitinib or are intolerant of sunitinib.
- Dose and Schedule:
 - 800 mg by mouth (PO) daily
- Toxicity:
 - Types of toxicity experienced are similar to other vascular endothelial growth factor (VEGF) tyrosine-kinase inhibitors (TKIs) but the frequency and grade may be different. LFTs should be frequently measured (at least once every two weeks initially) as they are often elevated with this drug.
- Efficacy Assessment:
 - Imaging of involved sites every 3 months initially then as clinically indicated. Patients responding with either stable disease or an objective response may continue therapy. Treatment is to be continued until disease progression or patient intolerance.

Second-line Therapy

Sorafenib (Escudier et al., 2006; Escudier et al., 2009; Ratain et al., 2006)

- Indication:
 - Second-line therapy after cytokine failure based on superior activity compared to best supportive care in a randomized phase III trial.
- Dose and Schedule:
 - Starting dose at 400 mg twice a day continuously. Each treatment cycle is 6 weeks in duration.
- Toxicity:
 - Physician must be aware of the toxicity profile of sorafenib and follow patients accordingly with experienced nursing support. Dose must be modified per individual's toxicity profile. Patient may be assessed every cycle for tolerance. Interval can be lengthened after 2 cycles if clinically appropriate.
- Efficacy Assessment:
 - Imaging every 2 cycles initially then as clinically indicated. Treatment is continued until disease progression or patient intolerance.

Everolimus

- Indication:
 - Standard of care as second-line therapy for metastatic RCC after progression on sunitinib, sorafenib, or both based on phase III data demonstrating superior progression-free survival than best supportive care.
- Dose and Schedule:
 - Starting dose at 10 mg/day orally
- Efficacy Assessment:
 - Imaging every 2 cycles (12 weeks) initially then as clinically indicated
 - Continue treatment until disease progression or patient intolerance.
- Toxicity:
 - Physician must be aware of the toxicity profile of everolimus and follow patients accordingly with experienced nursing support.
 - Dose must be modified as per individual's toxicity profile.
 - Patient must be assessed every cycle for tolerance; interval may be lengthened after 2 cycles if clinically appropriate.
 - Pneumonitis has been reported and should be monitored.

Local Therapy (Motzer et al., 2008)

Cytoreductive Nephrectomy Prior to or Following Targeted Therapy

- There is no data to guide clinical practices at this time. Decisions are to be made based on clinical indications. About 90% of enrolled patients had undergone a nephrectomy prior to systemic therapy in both the sunitinib and the sorafenib phase III trials.
- Nephrectomy has shown overall survival benefit when used in conjunction with interferon.
- Patients who appear to benefit most from nephrectomy are those with:
 - Most of the tumor burden within the kidney ($\geq 90\%$)
 - Good performance status
 - No central nervous or liver involvement (with rare exceptions)
 - Other considerations include:
 - Surgical resectability taking into consideration of morbidity to proximal vital structures, encasement of the renal hilum, and other complicating factors (Rini & Campbell, 2007; Heng & Kollmannsberger, 2009)

- Laparoscopic nephrectomy is the emerging standard surgical procedure whenever technically feasible.

Palliative Nephrectomy

Nephrectomy should be offered as a palliative procedure at any time when improvement of clinically meaningful symptoms can be achieved.

Renal Embolization

This approach can be offered as a palliative treatment for those with local symptoms but unable to undergo a nephrectomy.

Treatment to Metastatic Sites

Metastasectomy

In patients with limited and resectable metastatic disease surgical intervention can be considered. The clinical decision should be based on Eastern Cooperative Oncology Group (ECOG) status, size, and number of metastases. This can either be offered as the primary modality, or following systemic therapy. Timing of therapy is based on when metastases occur post-surgery.

Palliative Radiation

For symptomatic lesions, particularly metastases to bone, radiation therapy should be considered.

Bone Metastases

Bisphosphonates or other inhibitors of bone resorption may be considered as an adjunctive therapy.

Follow-up

- For those not on active treatments, follow-up as clinically indicated.
- If relapses are to occur, they may happen early or very late. Therefore, follow-up should continue for at least five years.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Renal cell carcinoma

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Nephrology

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To outline management decisions for renal cell carcinoma

Target Population

Men and women with renal cell carcinoma

Interventions and Practices Considered

Assessment/Evaluation

1. History and physical examination (lymph node survey)
2. Chest X-ray
3. Computed tomography (CT) of abdomen/pelvis/thorax with contrast
4. Magnetic resonance imaging
5. Laboratory testing (complete blood count, creatinine, calcium, liver function tests, renal function tests)
6. Biopsy (option as part of active observation or prior ablative therapy)
7. CT of chest, if T2 or T3
8. Bone scan, if T2, T3, or alkaline phosphatase is elevated

Management/Treatment

1. Active surveillance (as clinically indicated)
2. Surgical intervention
3. Minimally invasive therapy (radiofrequency ablation, cryoablation)
4. Follow up (history, physical examination, blood tests, chest X-ray, CT, ultrasound)
5. First line therapy (sunitinib, temsirolimus, pazopanib)
6. Second line therapy (sorafenib, everolimus)
7. Local therapy
 - Cytoreductive nephrectomy prior to or following targeted therapy
 - Palliative nephrectomy
 - Renal embolization
8. Treatment to metastatic sites
 - Metastasectomy
 - Palliative radiation
 - Bisphosphonates (or other inhibitors of bone resorption as adjunctive therapy for bone metastases)
9. Best supportive care (as clinically indicated)
10. Follow up

Major Outcomes Considered

- Overall survival

- Disease-free survival (early stage disease)
- Progression-free survival (advanced stage disease)
- 5-year mortality rate
- Adverse events associated with treatment
- Recurrence rate

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (patient or population, intervention, comparisons, outcomes).

Guideline Question

What are the appropriate management and follow up strategies for renal cell carcinoma?

Search Strategy

MEDLINE and EMBASE (1965 to August 2011) and clinical practice guideline databases, including the Cochrane Library and the National Guideline Clearinghouse, were searched for evidence relevant to this topic.

For the most recent update of this guideline, the search term "renal cell carcinoma" limited to human clinical trials published in English between August 2010 and August 2011 was used, resulting in 98 citations total. Articles were further excluded if they were phase I or included fewer than 10 renal cell carcinoma patients, were non-treatment related (i.e., pathology/staging, imaging, genetics, prevention, etc.), retrospective studies that did not include a comparison group, did not include adult patients, and did not look at survival, recurrence, or quality of life outcomes. This resulted in the exclusion of 68 studies.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#) (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the AGREE II instrument (<http://www.agreetrust.org>) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the [Guideline Utilization Resource Unit Handbook](#) (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team.

When the draft guideline document is completed, revised, and reviewed by the Knowledge Management Specialist and the working group members, it will be sent to all members of the Provincial Tumour Team for review and comment. The working group members will then make final

revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Director of Provincial Clinical Teams.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Atkins MB. Management of advanced renal cancer. *Kidney Int.* 2005 May;67(5):2069-82. [PubMed](#)

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, Negrier S, Chevreau C, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Anderson S, Hoflena G, Shan M, Pena C, Lathia C, Bukowski RM. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol.* 2009 Jul 10;27(20):3312-8. [PubMed](#)

Escudier B, Szczylik C, Demkow T, et al. Randomized phase II trial of the multi-kinase inhibitor sorafenib versus interferon (IFN) in treatment-naïve patients with metastatic renal cell carcinoma (mRCC) [abstract]. *J Clin Oncol.* 2006;24:217S.

Escudier BJ. A randomized, double-blind cross-over patient preference study of pazopanib versus sunitinib in treatment-naïve locally advanced or metastatic renal cell carcinoma (mRCC) [abstract]. In: 2010 ASCO Annual Meeting. Alexandria (VA): American Society of Clinical Oncology (ASCO); 2010.

Heng DY, Kollmannsberger C. State-of-the-art treatment of metastatic renal cell carcinoma. *Curr Oncol.* 2009 May;16 Suppl 1:S16-23. [PubMed](#)

Houk BE, Bello CL, Michaelson MD, et al. Exposure-response of sunitinib in metastatic renal cell carcinoma (mRCC): A population pharmacokinetic/pharmacodynamic (PKPD) approach. *J Clin Oncol.* 2007;25:5027.

Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawski E, Sosman J, McDermott D, Bodrogi I, Kovacevic Z, Lesovoy V, Schmidt-Wolf IG, Barbarash O, Gokmen E, O'Toole T, Lustgarten S, Moore L, Motzer RJ, Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007 May 31;356(22):2271-81. [PubMed](#)

Kassouf W, Siemers R, Morash C, Lacombe L, Jewett M, Goldenberg L, Chin J, Chetner M, Wood CG, Tanguay S, Aprikian AG. Follow-up guidelines after radical or partial nephrectomy for localized and locally advanced renal cell carcinoma. *Can Urol Assoc J.* 2009 Feb;3(1):73-6. [PubMed](#)

Motzer RJ, Escudier B, Oudard S, et al. RAD001 vs placebo in patients with metastatic renal cell carcinoma (RCC) after progression on VEGFr-TKI therapy: Results from a randomized, double-blind, multicenter phase-III study. *J Clin Oncol.* 2008;26S:LBA5026.

Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007 Jan 11;356(2):115-24. [PubMed](#)

Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE, Li JZ, Bello CL, Theuer CP, George DJ, Rini BI. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-

derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol. 2006 Jan 1;24(1):16-24. [PubMed](#)

Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, Redman BG, Margolin KA, Merchan JR, Wilding G, Ginsberg MS, Bacik J, Kim ST, Baum CM, Michaelson MD. Sunitinib in patients with metastatic renal cell carcinoma. JAMA. 2006 Jun 7;295(21):2516-24. [PubMed](#)

Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, Gore M, Desai AA, Patnaik A, Xiong HQ, Rowinsky E, Abbruzzese JL, Xia C, Simantov R, Schwartz B, O'Dwyer PJ. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2006 Jun 1;24(16):2505-12. [PubMed](#)

Rini BI, Campbell SC. The evolving role of surgery for advanced renal cell carcinoma in the era of molecular targeted therapy. J Urol. 2007 Jun;177(6):1978-84. [50 references] [PubMed](#)

Rini BI, George DJ, Michaelson MD, et al. Efficacy and safety of sunitinib malate (SU11248) in bevacizumab-refractory metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol. 2006;24:222S.

Rini BI, Tamaskar I, Shaheen P, Salas R, Garcia J, Wood L, Reddy S, Dreicer R, Bukowski RM. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst. 2007 Jan 3;99(1):81-3. [PubMed](#)

Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. Ann Oncol. 2008 Sep;19(9):1613-8. [PubMed](#)

Type of Evidence Supporting the Recommendations

For the most recent update of this guideline, the evidence was from human clinical trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of patients with renal cell carcinoma

Potential Harms

- Sunitinib: Most common grade 3 toxicities include hypertension, fatigue, diarrhea, and hand-foot syndrome. Cardiotoxicity has become an issue and in patients with pre-existing coronary artery disease (CAD) or CAD risk factors, monitoring of ventricular ejection fraction should be considered.
- Temsirolimus: Most common toxicities include rash, peripheral edema, hyperglycemia, and hyperlipidemia.
- Pazopanib: The most common adverse events were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting.
- Everolimus: The toxicity profile for everolimus includes infections, dyspnea, pneumonitis, and fatigue. Pneumonitis has also been reported.
- Sorafenib: The toxicity profile for sorafenib includes diarrhea, rash, fatigue, alopecia, and hand-foot skin reactions.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Genitourinary Tumour Team. Renal cell carcinoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2012 May. 14 p. (Clinical practice guideline; no. GU-003). [50 references]

Adaptation

Some of the recommendations in this guideline were adapted from the following guideline:

- Kassouf W, Siemens R, Morash C, Lacombe L, Jewett M, Goldenberg L, Chin J, Chetner M, Wood CG, Tanguay S, Aprikian AG. Follow-up guidelines after radical or partial nephrectomy for localized and locally advanced renal cell carcinoma. *Can Urol Assoc J*. 2009 Feb;3(1):73-6.

Date Released

2011 Jan (revised 2012 May)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

Alberta Health Services, Cancer Care

Guideline Committee

Renal Cell Carcinoma Working Group

Composition of Group That Authored the Guideline

Not stated

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services, Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Genitourinary Tumour Team. Renal cell carcinoma. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Jan. 15 p. (Clinical practice guideline; no. GU-003). [56 references]

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the [Alberta Health Services Web site](#) .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): Alberta Health Services, Cancer Care; 2011 Dec. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the [Alberta Health Services Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 10, 2012. The information was verified by the guideline developer on March

30, 2012. This NGC summary was updated by ECRI Institute on May 9, 2012.

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